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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,397	02/16/2001	Altaf A. Lal	6395-57049	4907

24197 7590 02/24/2004

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 02/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,397	LAL ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,10 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *3* is/are allowed.

6)☒ Claim(s) *1,5,6,10 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *2/11/04* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The after final amendment filed January 15, 2004 has been entered. Claim 1 has been amended. Claims 1, 3-6, 10 and 13 are pending and under examination in the application.

2. Upon further review and reconsideration, the finality of the rejection of the last Office Action, mailed October 15, 2003 is withdrawn and new rejections are set forth below:

Rejections Withdrawn

3. In view of Applicant's amendment and response the following rejections set forth in the Office action mailed October 15, 2002 have been withdrawn:

a) Rejection of claims 1, 3 5-6 and 13 under 35 U.S.C. 102(b), pages 2-4, paragraph 3 of the previous Office action.

b) Rejection of claims 1, 3, 5-6 and 13 under 35 U.S.C. 103(a), pages 4-6, paragraph 4 of the previous Office action.

c) Rejection of claim 10 under 35 U.S.C. 102(b), pages 6-9, paragraph 5 of the previous Office action.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 5-6 and 13 are rejected under 35 U.S.C. 103(a) as unpatentable Tine et al *(Infection and Immunity, Sept. 1996, p. 3833-3844)* in view of Gilbert et al, *(Nature Biotechnology, Volume 15, November 1997, p. 1280-1284).*

Claims 1, 5-6 and 13 are drawn to a single protein comprising peptides form two or more stages in a life cycle of *Plasmodium falciparum* wherein each peptide comprise an antigenic epitope comprising the amino acid sequence as set forth as SEQ ID Nos: 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25.

Tine et al teach the highly attenuated NYVAC vaccinia strain that has been utilized to develop a multi-antigen, multistage vaccine candidate for malaria. Tine et al teach a gene encoding seven *Plasmodium falciparum* antigens derived from the sporozoite, liver, blood and sexual stages of parasite lifecycle were inserted into a single NYVAC genome to generate NYVAC-Pf7. Tine et al teach that the genes that encode seven *Plasmodium falciparum* antigens are derived from circumsporozoite protein, sporozoite surface protein, liver stage antigen 1, merozoite surface antigen, serine repeat antigen, apical membrane antigen 1 (i.e. T cell epitope) and 25kDa

sexual-stage antigen. Tine et al teach that each of the seven antigens were expressed in HYVAC-Pf7-infected culture cells and the genotypic and phenotypic stability of the recombinant virus was demonstrated (see the Abstract). Tine et al suggest that a NYVAAC recombinant expressing a constellation of seven *P. falciparum* antigens could provide a vaccine candidate with the potential to elicit immunity directed against multiple stages in the malarial life cycle (page 3836, 2nd column).

Tine et al do not teach the specific peptides of the antigenic epitopes as set forth in the claimed amino acids sequences.

Gilbert et al teach recombinant Ty virus-like particles (Ty-VLPs) carrying a string of up to 15 defined cytotoxic T lymphocyte (CTL) epitopes from *Plasmodium* species (see the Abstract). Gilbert et al teach that it is possible to identify epitopes in conserved regions of several *P. falciparum* antigens to formulate a vaccine that may enable the immune system of the host to mount an effective immune response against most or all strains of *P. falciparum* (page 1280). Gilbert et al teach antigenic epitopes that have been used to create a candidate vaccine for *Plasmodium falciparum* malaria and suggest that there are several lines of evidence supporting a protective role for CTL against the liver-stage parasite in the immunity to malaria (page 1280). Gilbert et al teach liver stage epitopes Is6 and Is8 (page 1281, Table 1) that have the same amino acids sequences as SEQ ID Nos. 9 and 10, respectively of the claimed invention. Gilbert et al teach B cell epitopes from circumsporozoite (CS) protein (page 1281, Table 1) that have the same amino acid sequence as SEQ ID No: 4 of the claimed invention.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the antigenic epitopes from two or more life-stages in a single recombinant protein because Tine et al teach that single malarial antigens have failed to protect individuals from malaria and a way to mount a fully effective immune response would be to produce a vaccine that response to other antigen and life cycle stages, resulting in protective immunity (page 3833). Tine et al teach that a multi-antigen, multi-life cycle approach by which immune responses are elicited against multiple antigens of several of the life stages of the *P. falciparum* may be a more effective vaccination strategy (page 3833). Additionally, Gilbert et al has demonstrated that the use of multiple epitopes from different life stages of *Plasmodium falciparum* produce multi-functional epitopes which enables the immune response to be directed towards conserved regions of antigens, thereby preventing the pathogen from escaping or antagonizing the host CTL responses (page 1283). It would be expected barring evidence to the contrary, that a multi-antigen, multi-stage (including the sporozoite, liver, blood and sexual stages of *Plasmodium falciparum*) vaccine would be effective in treating and preventing *Plasmodium falciparum* malaria.

5. Claim 4 is rejected under 35 U.S.C. 103(a) as unpatentable over Tine et al in view of Gilbert et al as applied to claims 1, 5-6 and 13 above in further view of Schmitt et al *(Molecular Biology Reports Volume 18, 1993, p.223-230).*

Claim 4 is drawn to the recombinant protein of claim 1 and further comprising a signal peptide polyhistidine and a T-cell helper epitope.

The teachings of Tine et al and Gilbert et al have been described previously.

Tine et al and Gilbert et al as combined above do not teach the use of a polyhistidine.

Schmitt et al teach affinity purification of histidine-tagged proteins (see the Title). Schmitt et al teach that the expression of recombinant proteins is a standard technique in molecular biology and a wide variety of prokaryotic as well as eukaryotic expression systems are currently in use. Schmitt et al teach that a limiting step is often that the purification of the expressed recombinant protein that yield low expression levels are employed (see the Abstract). Schmitt et al teach that short amino acid sequences can be fused to the recombinant protein as a tag (page 223). Schmitt et al teach that a stretch of 6 histidine residues (His-tag) linked to the N- or C-terminal part of a recombinant protein is sufficient to allow a high expression of purified protein (page 229).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the histidine-tag as taught by Schmitt et al to the recombinant multi-antigen of Tine et al and Gilbert et al because Tine et al suggest

that a NYVAC recombinant expressing a constellation of seven *P. falciparum* antigens could provide a vaccine candidate with the potential to elicit immunity directed against multiple stages in the malarial life cycle (page 3836, 2nd column). It well known in the art to express, characterize and purify recombinant proteins. It is well known in the art to use signal proteins to express recombinant proteins and to use polyhistidine tags to purify recombinant proteins. Schmitt et al teach a stretch of 6 histidine residues (His-tag) linked to the N- or C-terminal part of a recombinant protein is sufficient to allow purification of the recombinant protein (page 229). It would have been expected barring evidence to the contrary, that the addition of a His-tag to recombinant proteins would allow for high expression of purified protein. The addition of the His-tag is well within the level of skill in the art.

6. Claims 1 and 10 are rejected under 35 U.S.C. 103(a) as unpatentable Tine et al *(Infection and Immunity, Sept. 1996, p. 3833-3844)* in view of Gilbert et al, *(Nature Biotechnology, Volume 15, November 1997, p. 1280-1284).*

Claim 10 is drawn to a protein composition comprising the recombinant protein of claim 1, in a pharmaceutically acceptable carrier.

Tine et al teach the highly attenuated NYVAC vaccinia strain that has been utilized to develop a multi-antigen, multistage vaccine candidate for malaria. Tine et al teach a gene encoding seven *Plasmodium falciparum* antigen derived from the sporozoite, liver, blood and sexual stages of parasite lifecycle were inserted into a single NYVAC genome to generate NYVAC-Pf7. Tine et al teach that the genes that

encode seven *Plasmodium falciparum* antigens are derived from circumsporozoite protein, sporozoite surface protein, liver stage antigen 1, merozoite surface antigen, serine repeat antigen, apical membrane antigen 1 (i.e. T cell epitope) and 25kDa sexual-stage antigen. Tine et al teach that each of the seven antigens were expressed in HYVAC-Pf7-infected culture cells and the genotypic and phenotypic stability of the recombinant virus was demonstrated (see the Abstract). Tine et al suggest that a NYVAAC recombinant expressing a constellation of seven *P. falciparum* antigens could provide a vaccine candidate with the potential to elicit immunity directed against multiple stages in the malarial life cycle (page 3836, 2nd column).

Tine et al do not teach the specific peptides of the antigenic epitopes as set forth in the claimed amino acids sequences nor do Tine et al specifically teach the use of pharmaceutically acceptable carrier.

Gilbert et al teach recombinant Ty virus-like particles (Ty-VLPs) carrying a string of up to 15 defined cytotoxic T lymphocyte (CTL) epitopes from *Plasmodium* species (see the Abstract). Gilbert et al teach that it is possible to identify epitopes in conserved regions of several *P. falciparum* antigens to formulate a vaccine that may enable the immune system of the host to mount an effective immune response against most or all strains of *P. falciparum* (page 1280). Gilbert et al teach antigenic epitopes that have been used to create a candidate vaccine for *Plasmodium falciparum* malaria and suggest that there are several lines of evidence supporting a protective role for CTL against the liver-stage parasite in the immunity to malaria (page 1280). Gilbert et al further teach antigenic epitopes that comprise a heparin binding motif and epitopes that

could impair the ability of sporozoites to invade hepatocytes (page 1282). Gilbert et al teach liver stage epitopes Is6 and Is8 (page 1281, Table 1) that have the same amino acids sequences as SEQ ID Nos. 9 and 10, respectively of the claimed invention. Gilbert et al teach B cell epitopes from circumsporozoite (CS) protein (page 1281, Table 1) that have the same amino acid sequence as SEQ ID No: 4 of the claimed invention. Gilbert et al teach that the protein particle vaccine containing multiple malaria epitopes was resuspended in PBS (pharmaceutically acceptable carrier) for injection (page 1283).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use a pharmaceutical acceptable carrier to administer the multi-antigen to a subject because Gilbert et al teach that the protein particle vaccine containing multiple malaria epitopes was resuspended in PBS (pharmaceutically acceptable carrier) for injection (page 1283). It is well known in the art to use pharmaceutical acceptable carriers to administer vaccines.

Status of Claims

7. Claim 3 appears to be free of the cited prior art.

Conclusion

8. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Vanessa L. Ford
Biotechnology Patent Examiner
February 13, 2004

NITA MINNIFIELD
PRIMARY EXAMINER
2/18/04